Original Article

Diabetes Mellitus, Hypertension, Hyperlipidemia and Obesity do not Affect Tumor Expression of Estrogen and Progesterone Receptors in Saudi Breast Cancer Patients

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ABSTRACT

Objective: To evaluate the relationship between estrogen and progesterone receptor status and the presence of diabetes mellitus, hypertension, obesity or dyslipidemia
Design: Retrospective study
Setting: Department of Oncology, King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia
Subjects: A hundred and twelve Saudi patients diagnosed with breast cancer, admitted to King Khalid University Hospital (KKUH) between 2000 and 2006
Intervention: Fine needle or true cut biopsy
Main outcome measure: Association between tumor receptor status and the presence of comorbidity
Results: There was no relationship between estrogen receptors and progesterone receptors expression and the presence of diabetes mellitus, dyslipidemia, hypertension or obesity. Hypertension was associated with HER2/neu positivity (p = 0.045, OR = 2.817, CI 95% (1.023 - 7.754)). Hypertensive patients were also found to present with earlier clinical T-stages (p = 0.045).
Conclusion: Expression of estrogen and progesterone receptors was not affected by the presence of diabetes mellitus, dyslipidemia, hypertension or obesity. However, our findings suggest that hypertension is related to HER2/neu positivity. Hypertensives were also more likely to present with earlier clinical T stages than non-hypertensives.

KEY WORDS: breast cancer, estrogen receptor, metabolic syndrome X, ErbB-2 receptor, TNM stage

INTRODUCTION

Breast cancer is the most common type of cancer in females, and is the fifth leading cause of cancer related deaths worldwide[1]. The issue is particularly pressing in Saudi Arabia, where it is ranked as the most commonly diagnosed type of cancer, accounting for 15% of all cancer incidences[2]. It is the most common cancer in Saudi female patients with a prevalence of 28.8%[2].

Different risk factors have been linked to the development of the disease, such as age, family history, use of contraceptives, early menarche, and late menopause[3]. The rising prevalence of metabolic diseases in Saudi Arabia is alarming. In 2014, the WHO reported that the average body mass index (BMI) in Saudi women was found to be 28.7, and the prevalence of obesity was 41.4%[4]. The prevalence of raised blood pressure was 21.8% and the prevalence of raised blood glucose was 18.3%[4]. Dyslipidemia was reported to be prevalent in between 25 to 44% of Saudis, depending on the type of dyslipidemia[5].

A case-control study conducted in 2013 suggests that obesity might be a risk factor for developing breast cancer[3,6]. Another case-control study shows that hypertension might impact the risk for developing breast cancer, potentially affected by menopausal status[7,8]. Diabetes significantly increased the risk for developing breast cancer[7,9,10,11]. Also, low levels of high density lipoprotein cholesterol (HDL-C) might increase the risk of breast cancer development[12].

Breast cancer is classified based on multiple characteristics including pathologic, histologic and molecular features. Molecular features are further subtyped by immunohistochemical detection of

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hormonal receptors including estrogen, progesterone and the human epidermal growth factor receptor (HER2/neu). Estrogen and progesterone positive breast cancers are associated with benign outcomes and respond well to Tamoxifen and aromatase inhibitors[13-15]. HER2 positive tumors, on the other hand, are biologically aggressive but still manageable with targeted monoclonal antibody therapy against the receptors[16,17].

In light of this, studying the development of hormone receptors in breast cancer and their associated risk factors is essential to the management of the disease. However, more research is needed to link hormone receptor status in breast cancer with different comorbidities (hypertension, diabetes mellitus, dyslipidemia and obesity). This study aimed to assess the relationship between estrogen and progesterone receptor status and the presence of diabetes mellitus, hypertension, obesity or dyslipidemia at diagnosis.

SUBJECTS AND METHODS

A hundred and twelve Saudi patients diagnosed with breast cancer, admitted to King Khalid University Hospital (KKUH) between 2000 and 2006, were available for this retrospective cross-sectional secondary data analysis study. Data was obtained from the oncology department at KKUH. They underwent either breast conserving surgery with axillary lymph node dissection or modified radical mastectomy after neoadjuvant chemotherapy and radiotherapy. The inclusion criterion was histopathologically confirmed breast cancer. Exclusion criteria were: (1) male sex, and (2) incompletion of the above listed treatment regimen. A hundred and ten patients met the criteria. Formal consent to conduct this study was obtained from the Institutional Review Board Committee (IRB).

Clinical variables

Clinical features recorded for this study included; age, presence of comorbidities, body mass index, menopausal status, tumor hormone receptor status, TNM staging, and tumor grade.

Comorbidities considered for the study were diabetes mellitus, hypertension, dyslipidemia and obesity. Diabetes Mellitus was defined as fasting blood glucose ≥ 126 mg/dL. Hypertension was defined as a blood pressure reading over 140/90 mmHg, measured on 2 different occasions. Dyslipidemia was defined as elevated total cholesterol (> 240 mg/dL), high levels of low-density lipoprotein cholesterol (LDL-C) (>160 mg/dL), or low levels of high-density lipoprotein cholesterol (HDL-C) (<40 mg/dL). Obesity was defined as a BMI ≥ 30.

Tumor estrogen and progesterone receptor statuses were evaluated at the time of presentation using immunohistochemical analysis with antibodies against the estrogen receptors (Dako, Glostrup, Denmark) and progesterone receptors (BioGenex, San Ramon, CA, USA). A cutoff value of 1% for both receptors was considered positive, as per institutional protocol. HER2/neu overexpression was assessed using immunohistochemical equivocal cases using a HER2 DNA Probe Kit (Abbott Laboratories, Abbott Park, IL, USA). A HER2:CEP17 ratio of 2:1 or higher was considered HER2/neu positive.

Breast cancer diagnosis was made by examining either fine needle aspiration or TruCut biopsies, and correlated with clinical and radiological findings. Staging was done in accordance with the American Joint Committee on Cancer's TNM classification, 5th edition. The tumor grade was assessed by the modified Scarff-Bloom-Richardson grading system. Tumor size was estimated using the TNM clinical T stage, where T1: < 2 cm, T2: > 2 cm but ≤ 5 cm and T3: > 5 cm, all in the largest dimension. T4 was defined as any size with direct extension to the chest wall and/or to the skin.

Statistical Analysis

Patient characteristics were summarized using frequency, percentage, mean and standard deviation (SD). Fisher's exact test was used to study the associations among the estrogen, progesterone and HER2/neu receptor expression and comorbidities, adjusted for confounding factors with logistic regression. Associations between clinical T-stage and comorbidities were estimated using the Kendall's Tau test. A P-value < 0.05 with a confidence interval of 95% was considered statistically significant. Statistical analyses were executed using SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Macintosh, Version 21.0. Armonk, NY: IBM Corp.)

RESULTS

Patient Characteristics

A hundred and ten Saudi females were included in the analysis. Mean age was 47 years (SD ± 10). Premenopausal women comprised the majority of subjects, totaling 91 patients (82.7%). Mean BMI was 32 kg/m^2 (SD ± 7.16) and obesity was prevalent in 62 patients (56.4%). The most common histological subtype in this cohort was intraductal carcinoma (IDC), present in 93 patients (87.7%). A total of 51 patients (46.4%) were estrogen positive, 42 (38.2%) were progesterone positive and 64 (58.2%) were HER2/neu positive. Comorbidities were recorded in 75 patients (68.2%) (Table 1).

Table 1: Patient characteristics

Characteristics	n (%)	Mean (± SD)
Age groups		
< 25	2 (1.8)	23 (±0)
25 - 35	13 (11.8)	32 (±3)
36 - 45	29 (26.4)	40 (±3)
> 45	66 (60)	53 (±7)
Total	110 (100)	47 (±10)
BMI groups		
Below 18.5	1 (0.9)	15.7 (±0)
18.5 - 24.99	17 (15.5)	22.4 (±1.87)
25 - 29.99	30 (27.3)	27.8 (±1.35)
30 and above	62 (56.4)	36.92 (±5.16)
Total	110 (100)	32.00 (±7.16)
Menopausal status		
Premenopausal	91 (82.7)	
Postmenopausal	19 (17.3)	
Total	110 (100)	
Hormone receptors		
Estrogen		
Negative	59 (53.6)	
Positive	51 (46.4)	
Total	110 (100)	
Progesterone		
Negative	68 (61.8)	
Positive	42 (38.2)	
Total	110 (100)	
HER2		
Negative	46 (41.8)	
Positive	64 (58.2)	
Total	110 (100)	
Comorbidities		
DM		
No DM	86 (78.2)	
DM	24 (21.8)	
Total	110 (100)	
HTN		
No HTN	80 (72.7)	
HTN	30 (27.3)	
Total	110 (100)	
Dyslipidemia		
No dyslipidemia	99 (90)	
Dyslipidemia	11 (10)	
Total	110 (100)	
Obesity		
Not obese	48 (43.6)	
Obese	62 (56.4)	
Total	110 (100)	
Clinical T stage		
T1	35 (31.8)	
T2	44 (40)	
T3	20 (18.2)	
T4	9 (8.2)	
Missing	2 (1.8)	
Total	110 (100)	
Clinical N stage		
N0	49 (44.5)	
N1	35 (31.8)	
N2	14 (12.7)	
N3	12 (10.9)	
Total	110 (100)	
Clinical M stage		
0	81 (73.6)	
1	29 (26.4)	
Total	110 (100)	

Analysis

No significant findings were noted among the expression of estrogen or progesterone receptors and presence of diabetes mellitus, dyslipidemia, hypertension or obesity. No significance was found after adjusting for confounders.

Hypertension was associated with HER2/neu positivity ($p = 0.020$). The relationship was still significant after adjusting for confounding factors ($p = 0.045$, OR = 2.817 (1.023 - 7.754)). No other significant associations were found among HER2/neu expression and diabetes mellitus, dyslipidemia or obesity (Table 2).

Hypertensive patients were also found to present with earlier clinical T-stages when compared to non-hypertensives ($p = 0.045$). Diabetes mellitus, dyslipidemia and obesity did not show any correlation with the clinical T-stage (Table 3).

DISCUSSION

We did not find any statistically significant associations linking the expression of estrogen and progesterone receptors, with the presence of diabetes mellitus, hypertension, dyslipidemia or obesity. Relationships among HER2/neu expression and the presence of comorbidities were also investigated. It was observed that hypertensive patients were more likely to have HER2/neu positive tumors, an effect that was not observed with the other comorbidities. A decreasing trend in clinical T stage among patients with hypertension was noted. Hypertensives tended to present with earlier clinical T stages (T1, T2) than non-hypertensives.

Our findings on estrogen and progesterone receptors are similar to what was found in a study conducted in southwest China, which showed that diabetes mellitus did not affect estrogen and progesterone receptor expression[18]. Another study also demonstrated that hyperglycemia, hypertension, obesity and dyslipidemia had no effect on estrogen receptor expression[19]. A 2013 study found that postmenopausal patients with a BMI > 25 showed a higher incidence of estrogen positive and progesterone positive tumors[20]. Interestingly enough, the same study found breast cancer receptor expression was not influenced by BMI in premenopausal women, a finding that corroborates ours, given that 82% of our sample is premenopausal.

There remains some contradictory evidence in the literature. Breast cancer data from a 2003 Nurses' Health Study showed that patients with type 2 diabetes mellitus were found to have an increased risk of developing estrogen positive tumors[21]. BMI has been associated with receptor expression. Increased BMI was linked to increased expression of estrogen

Table 2: Relationship between receptor status and associated comorbidity

Comorbidity	Unadjusted P-value			Adjusted* P-value, OR (95%CI)					
	ER+	PR+	Her2-Neu+	ER+		PR+		Her2-Neu+	
Hypertension	0.371	0.497	0.020†	0.246	1.79 (0.66 - 4.82)	0.348	1.60 (0.98 - 4.28)	0.045†	2.81 (1.02 - 7.75)
Diabetes Mellitus	0.602	0.581	0.068	0.592	0.72 (0.22 - 2.32)	0.503	0.66 (0.20 - 2.18)	0.131	0.40 (0.12 - 1.13)
Obesity	0.150	0.790	0.453	0.168	0.58 (0.26 - 1.25)	0.853	0.92 (0.42 - 2.04)	0.264	1.59 (0.70 - 3.59)
Dyslipidemia	0.949	0.896	0.372	0.841	0.84 (0.16 - 4.40)	0.905	0.90 (0.16 - 4.83)	0.351	0.44 (0.08 - 2.44)

OR = Odds ratio; CI = Confidence interval; ER = Estrogen receptor; PR = Progesterone receptor; Her2-Neu = human epidermal growth factor receptor

* Adjusted for obesity, diabetes, hypertension and dyslipidemia

† Designates significant values. P <0.05

and progesterone receptors in postmenopausal breast cancer patients[22-24], while a meta-analysis demonstrated that obese women are more likely to develop triple-negative breast cancer[25].

Table 3: Relationship between comorbidities and clinical T stage

Comorbidity	Clinical T stage					P-value
	T1 n (%)	T2 n (%)	T3 n (%)	T4 n (%)	Total N (%)*	
Diabetes mellitus	8 (34)	6 (26)	5 (21)	4 (17)	23 (21)	0.481
Hypertension	15 (50)	9 (30)	4 (13)	2 (7)	30 (27)	0.045†
Dyslipidemia	6 (54)	3 (27)	2 (18)	0 (0)	11 (10)	0.141
Obesity	17 (28)	28 (46)	11 (18)	4 (7)	60 (55)	0.764

* Total sample size is 108; † Designates significant values; P < 0.05

The effect of hypertension on the expression of HER2/neu has not been described in the literature, to the best of our knowledge. A prospective study associated high levels of low density lipoprotein cholesterol (LDL-C) with HER2/neu positivity[26]. Our findings regarding diabetes mellitus and obesity with HER2/neu expression are consistent with findings in aforementioned studies[18,19].

We aimed to identify possible factors implicated in hormone receptor expression. The significance of this association lies in the ability to create prediction models of receptor expression patterns in breast cancer, which could be of use in policymaking and resource management. Although these results are observational, we cannot exclude the possibility that there are underlying mechanisms that remain unknown. Prospective studies would help to establish causality and temporality of the relationships, as opposed to our retrospective design. Other limitations of our study are the small sample size, lack of data regarding the severity and management of the diseases studied and the inability to account for important confounders. Although we accounted for the occurrence of multiple comorbidities (diabetes mellitus, hypertension, dyslipidemia and obesity), we were not able to account for other confounding factors such as occurrence of multiple receptors, menopausal status and estrogen exposure.

Future work should be guided towards identifying biological factors influencing receptor expression. Special attention should be devoted to the factors affecting occurrence of multiple receptor and triple negative breast cancers, as these have not been investigated thoroughly.

CONCLUSION

We did not find a relationship among diabetes mellitus, obesity and dyslipidemia with clinical T stage. In contrast, the southwest China study found that diabetics had larger tumor sizes in comparison to non-diabetics[18]. A different study found the same to be true of patients with high BMI[19]. Furthermore, high LDL-C was associated with larger tumors sizes[26]. Our result linking hypertension with lower clinical T-stage has not been described previously in the literature.

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